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Pharmacokinetics and Safety of Intravenous Cidofovir for Life-Threatening Viral Infections in Pediatric Hematopoietic Stem Cell Transplant Recipients

Amy E. Caruso Brown,[a]* Mindy N. Cohen,[b] Suhong Tong,[c] Rebecca S. Braverman,[d] James F. Rooney,[e] Roger Giller,[a] Myron J. Levin[f]

Section of Hematology, Oncology and Bone Marrow Transplantation, Department of Pediatrics, University of Colorado Denver Anschutz Medical Campus, Aurora, Colorado, USA[a]; Department of Anesthesiology, University of Colorado Denver Anschutz Medical Campus, Aurora, Colorado, USA[b]; Department of Biostatistics and Informatics, Colorado School of Public Health, University of Colorado Denver Anschutz Medical Campus, Aurora, Colorado, USA[c]; Department of Ophthalmology, University of Colorado Denver Anschutz Medical Campus, Aurora, Colorado, USA[d]; Gilead Sciences, Foster City, California, USA[e]; Section of Pediatric Infectious Diseases, Department of Pediatrics, University of Colorado Denver Anschutz Medical Campus, Aurora, Colorado, USA[f]

Children undergoing hematopoietic stem cell transplantation (HSCT) are at risk for life-threatening viral infections. Cidofovir is often used as a first-line agent for adenovirus infections, despite the absence of randomized controlled trials with HSCT patients, and as a second-line agent for resistant herpesvirus infections. The frequency and severity of adverse effects, particularly nephrotoxicity, in pediatric HSCT recipients are unclear, and pharmacokinetics (PK) of cidofovir in children have not previously been reported. This study was an open-label, nonrandomized, single-dose pilot study to determine the safety and PK of cidofovir in pediatric HSCT recipients with symptomatic adenovirus, nucleoside-resistant cytomegalovirus (CMV) or herpes simplex virus (HSV), and/or human papovavirus infections. Subsequent dosing and frequency were determined by clinical response and side effects, as assessed by the treating physician. Blood and urine samples were obtained from patients for PK studies and assessment of toxicity and virologic response. Twelve patients were enrolled (median age, 9 years; 33.5 days posttransplantation). Four of seven patients with adenovirus infection were successfully treated and eventually cleared their infections. Four of twelve patients died of disseminated viral disease and multiorgan failure. Two of twelve patients had evidence of acute kidney injury after the first dose, and one of these patients developed chronic kidney disease; two other patients developed late nephrotoxicity. The mean drug half-life was 9.5 h. There was no correlation between nephrotoxicity and plasma maximum concentration, clearance, or half-life. PK were similar to those reported for adults, although the drug half-life was significantly longer than that for adults. Cidofovir was well tolerated in the majority of patients. However, effective therapeutic strategies are urgently needed to support patients until immune reconstitution is achieved.

Autologous and allogeneic hematopoietic stem cell transplantation (HSCT) for the treatment of malignant and nonmalignant hematological and immunological disorders results in a variable period of compromised immunity (1). T-lymphocyte numbers and function are decreased by chemotherapeutic conditioning regimens, certain stem cell processing techniques, and immunosuppressive agents used to prevent or treat graft-versus-host disease (GVHD) in allogeneic HSCT recipients (1). In addition, the graft source, such as cord blood, peripheral blood stem cells, or marrow, impacts the pace and quality of immune reconstitution. Consequently, children undergoing HSCT are at profound risk for serious and potentially fatal viral infections. Viruses that commonly complicate HSCT include adenoviruses, cytomegalovirus (CMV), herpes simplex virus (HSV), human herpesvirus 6 (HHV-6), BK virus, and other community-acquired respiratory and gastrointestinal (GI) viruses (2–6). Furthermore, the need for protracted antiviral therapy due to impaired immune clearance increases the risk of antiviral resistance to first-line agents (4).

Cidofovir {1-[(*S*)-3-hydroxy-2-(phosphonomethoxy)propyl] cytosine dihydrate} is often used during HSCT as a second-line agent for the treatment of resistant herpesvirus infections, including HSV, CMV, and HHV-6 (7). In addition, while there are no randomized controlled trials to demonstrate the efficacy of cidofovir for treatment of adenovirus infection complicating HSCT, many programs use cidofovir as a first-line therapy for this opportunistic infection. Reported case series and retrospective studies have included sample sizes ranging from 8 to 43 pediatric patients, with widely varying favorable response (24 to 100%) and mortality (0 to 84%) rates (3, 4, 8–10). The new agent brincidofovir (CMX001) also may have efficacy in adenovirus treatment (11).

Cidofovir is a nucleoside phosphonate analogue that decreases viral DNA synthesis after incorporation into the nascent chain. Cidofovir is activated by intracellular kinases to a diphosphorylated form. When administered intravenously, >90% of the drug is excreted unchanged in the urine within 24 h through a combination of filtration and tubular secretion. In spite of this rapid

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Address correspondence to Amy E. Caruso Brown, aecbrown@gmail.com.

* Present address: Amy E. Caruso Brown, Center for Bioethics and Humanities and Division of Pediatric Hematology/Oncology, Department of Pediatrics, SUNY Upstate Medical University, Syracuse, New York, USA.

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TABLE 1 Characteristics of patients receiving cidofovir

Parameter[a]	Value
Median age of patients (yr) (range)	9 (2–14)
Median no. of days posttransplantation (range)	33.5 (12–111)
No. of patients	
Sex	
F	1
M	11
Type of transplant	
Allo	11
UCBT	10
MRD	1
Auto	1
Indication for transplant	
Hematologic malignancy	8
AML or MDS	5
ALL	3
Metastatic solid tumor	1
NBL	1
Nonmalignant disorder	3
Hemoglobinopathy	2
SCID	1
Primary viral indication for study enrollment	
AdV	7
BK virus	4
CMV	1

[a] F, female; M, male; Allo, allogeneic; UCBT, unrelated cord blood transplant; MRD, matched related donor; Auto, autologous; AML, acute myeloid leukemia; MDS, myelodysplastic syndrome; ALL, acute lymphoblastic leukemia; NBL, neuroblastoma; SCID, severe combined immunodeficiency; AdV, adenovirus.

elimination, cidofovir persists intracellularly, producing prolonged antiviral effects (9, 10, 12).

The major adverse effect of cidofovir, nephrotoxicity, occurs because it is taken up rapidly by proximal tubular cells by organic anion transporters at their antiluminal (basolateral) membrane but secreted into the lumen slowly, resulting in high intracellular drug concentrations that can cause tubular necrosis. Hyperhydration, together with coadministration of probenecid, has a nephroprotective effect. Probenecid, an organic acid, acts as a competitor of cidofovir for the transporter, thereby decreasing intracellular levels of cidofovir in renal tubular cells and increasing cidofovir plasma levels (9, 10, 12).

The prolonged intracellular half-life ($t_{1/2}$) achieved in human cells is the basis for the commonly used weekly administration schedule; however, the relationship between intracellular cidofovir concentrations and serum levels has not been determined (13). Pediatric dosing of cidofovir and supportive care guidelines for administration have been based on recommendations for use in adults, and studies have also varied in the specific treatment regimens used (8, 14).

The frequency and severity of cidofovir-related side effects, particularly nephrotoxicity, in pediatric HSCT recipients are unclear. In one retrospective study, 3 out of 10 pediatric HSCT recipients treated with cidofovir developed at least a 50% increase in serum creatinine levels (13). Thus, the primary objectives of this report were to determine the safety and pharmacokinetics (PK) of cidofovir injection in children with life-threatening viral infections following HSCT.

MATERIALS AND METHODS

Patients. Eligible patients were enrolled at the Children's Hospital Colorado. Inclusion criteria for enrollment were (i) age of 6 months to <18 years; (ii) an HSCT within 2 years of study entry; and (iii) symptomatic infection with adenovirus, nucleoside-resistant CMV, human papovavirus (BK or JC virus), and/or nucleoside-resistant HSV, diagnosed by viral culture or PCR. Relevant exclusion criteria were (i) hematology, blood chemistry, or urinalysis results that were >10% outside the normal range and not attributable to bone marrow recovery post-HSCT or to viral infection; (ii) participation in another clinical drug trial within 30 days of enrollment; (iii) clinically significant hypersensitivity to sulfa-type drugs or probenecid; (iv) inability to swallow oral medication (probenecid); (v) use of cidofovir within 14 days of enrollment; or (vi) a serum creatinine level >2 times the upper limit of normal for age or a glomerular filtration rate (GFR) of <60 ml/min/1.7 m^2, as assessed by radionuclide GFR, 24-h urine creatinine clearance, or calculated creatinine clearance.

Design. This was an open-label, nonrandomized, single-dose pilot study to determine the safety and PK of cidofovir injection. Subsequent dosing and frequency were determined by clinical response and side effects, as assessed by the treating physician. Screening prior to enrollment included measurement of the complete blood count with differential (CBC), prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen, serum electrolytes, blood urea nitrogen, creatinine, liver function, uric acid, and lactic dehydrogenase (LDH); urinalysis (UA); urine pregnancy test; virologic studies (quantitative viral load by PCR on blood

TABLE 2 Characteristics of individual patients receiving cidofovir in the trial

Patient	Age (yr)/sex	Indication for transplant[a]	Type of transplant	Primary clinical indication for study enrollment	Day posttransplant at enrollment
1	4/M	AML	Allo/UCBT	AdV enteritis	+55
2	10/M	AML	Allo/UCBT	BK virus hemorrhagic cystitis	+26
3	2/M	NBL	Auto	Disseminated AdV	+12
4	9/M	MDS	Allo/UCBT	BK virus hemorrhagic cystitis	+40
5	9/M	AML	Allo/UCBT	BK virus hemorrhagic cystitis	+22
6	4/F	AML	Allo/UCBT	BK nonhemorrhagic cystitis	+46
7	10/M	SCD	Allo/MRD	AdV enteritis	+27
8	14/M	ALL	Allo/UCBT	AdV enteritis	+111
9	13/M	ALL	Allo/UCBT	AdV enteritis	+94
10	11/M	ALL	Allo/UCBT	AdV viremia	+12
11	2/M	SCID-NEMO	Allo/UCBT	AdV viremia	+56
12	3/M	Beta-thal	Allo/UCBT	CMV viremia	+27

[a] SCD, sickle cell disease; Beta-thal, beta-thalassemia major.

TABLE 3 Early outcomes of cidofovir therapy[c]

Patient	Primary virus (source)	Viral copy no./ml by PCR at study entry	Viral copy no./ml by PCR after first dose[a]	Toxicity observed after first dose	Viral coinfection(s)[b]
1	AdV (blood)	1,568	12,750	None	RSV
3	AdV (blood)	>1,000,000	>1,000,000	None	None
7	AdV (blood)	11,815	100–1,000	None	BK virus
8	AdV (blood)	3,524	12,635	AKI (injury)	CMV, BK virus
9	AdV (blood)	>1,000,000	>1,000,000	None	BK virus, HHV-6
10	AdV (blood)	100–1,000	100–1,000	None	BK virus, RSV, HZ virus
11	AdV (blood)	359,575	7,651	None	CMV
2	BK virus (urine)	>1,000,000	>1,000,000	None	HHV-6, AdV
4	BK virus (urine)	>100,000,000	>100,000,000	AKI (risk)	AdV
5	BK virus (urine)	>100,000,000	>100,000,000	None	CMV
6	BK virus (urine)	>100,000,000	42,000,000	None	CMV
12	CMV (blood)	14,743	63,914	None	None

[a] Approximately 6 days after the first dose.
[b] Present at study entry or diagnosed during the study.
[c] RSV, respiratory syncytial virus; AKI, acute kidney injury (RIFLE criteria for staging); HZ, herpes zoster.

or urine); and measurement of radionuclide GFR or 24-h creatinine clearance. Consenting patients received a cidofovir injection (5 mg/kg of body weight) as a 1-h infusion on day 1 of the study. Dosages were adjusted for renal function according to the package insert. Oral probenecid at a dose of 25 mg/kg was given 3 h prior to the scheduled cidofovir infusion; probenecid (10 mg/kg) was given 2 h and 8 h postinfusion. Prehydration and posthydration were performed with a 1-h normal saline infusion (10 ml/kg) prior to and 1 h after the cidofovir infusion. Patients receiving acyclovir had it held on the day of the cidofovir infusion and for 4 days afterwards. Those receiving twice-daily cyclosporine or tacrolimus had the evening dose held on the day of cidofovir infusion.

Safety monitoring. Blood and urine samples were obtained prior to cidofovir administration on day 1 and on days 3, 6, 8, 14, 22, 28, and 60 following cidofovir infusion. These samples were used for measurements of CBC, PT, PTT, serum chemistry, liver function, LDH, and uric acid and for UA. Ophthalmoscopic examination, including measurement of intraocular pressure, was performed on day 6. Virologic studies were performed on days 1, 6, 14, and 60 and as clinically indicated.

Statistical methods. Patients' clinical characteristics were summarized by using descriptive statistics. Means and standard deviations were used to summarize continuous variables, while counts and percentages were used to describe categorical variables. R version 3.0.1 was used to perform the analysis (15).

Pharmacokinetic analysis. Blood samples for PK studies were obtained from all subjects at eight time points: on days 1 and 2 prior to cidofovir infusion and 1, 2, 4, 6, 12, 24, and 48 h postinfusion. Urine samples were obtained from seven subjects at five time points: prior to infusion and 0 to 4, 4 to 8, 8 to 12, and 12 to 24 h postinfusion on day 1.

Cidofovir concentrations in EDTA-treated plasma were measured by using a validated liquid chromatography-tandem mass spectrometry method according to procedures described previously by Momper et al. (16). Prestudy validation met all acceptance criteria set forth by applicable guidance by the U.S. Food and Drug Administration (17). As for the original method, the assay was linear from 20 to 1,000 ng/ml. No significant matrix interferences (<20% of signal at the lower limit of quantification), matrix effects (ion suppression/ion enhancement), and carryover were detected. Quality control (QC) samples analyzed during study sample analysis showed that imprecision at all three QC concentration levels was 10% and that accuracy was between 90 and 110%. All calibration curves used for study sample quantification were linear, with an r^2 value of >0.98.

The plasma concentration data from 12 subjects were used to develop a model for evaluation of individual PK parameters. Plasma cidofovir concentration-versus-time data were fitted on an individual basis with 1- and 2-compartment PK models with the SAAM II software system (SAAM Institute, Seattle, WA), using a previously described relative error model (26). The parameters of the model were defined as plasma clearance (CL_e) (milliliters per kilogram per minute), volume of the central compartment (V_1) (milliliters per kilogram), volume of the peripheral compartment (V_2) (milliliters per kilogram), and intercompartmental clearance (CL_I) (milliliters per kilogram per minute). The steady-state volume of distribution (V_{ss}) (milliliters per kilogram) was defined as the sum of V_1 and V_2. Data were weighted by the reciprocal of their standard deviation, assuming a fractional standard deviation of 0.5. After visual inspection for model misspecification of the measured and predicted plasma concentration-versus-time relationships, the 2-compartment model was selected over the 1-compartment model by using the Akaike information criterion and the Schwarz criterion. Estimates of terminal elimination half-lives were determined from the exponential decay constant of the fitted function between intervals of 40 to 44 h and 45 to 48 h to verify constancy.

Given the wide heterogeneity of the small sample size and incomplete data on measures such as creatinine clearance, no meaningful covariates could be obtained from a population PK analysis, so we analyzed and reported kinetic parameters for each patient by standard 2-step methods.

To analyze the urine concentration data, a normal physiologic urine flow rate of 1 ml/kg/h (0.0167 ml/kg/min) was assumed, since urine volume was not recorded during sample collection. Under this assumption, renal clearance of cidofovir (milliliters per kilogram per minute) was calculated by multiplying the ratio of the urine concentration to the plasma concentration by the assumed urine flow rate.

Ethical approval and funding. This study was approved by the Colorado Multiple Institutional Review Board. Written informed consent was obtained from the parents of all patients. Gilead Sciences, Inc., funded the study.

RESULTS

Characteristics of enrolled patients are summarized in Table 1 and presented for individual patients in Table 2. Twelve patients were enrolled, ranging in age from 2 to 14 years (median, 9 years), at 12 to 111 days posttransplantation (median, 33.5 days). Eleven transplants were allogeneic, 10 of which were unrelated cord blood transplants. Nine of the 12 transplants were performed for malignant indications. Seven patients had adenovirus viremia as the primary indication for treatment with cidofovir, four had BK virus viruria, and one had CMV viremia. All patients were symptomatic, although three had only fever without another source when the viral infection was identified. Specific clinical symptoms at study enrollment are included in Table 2.

TABLE 4 Later outcomes of cidofovir therapy[a]

Primary virus and patient	Source of primary virus	No. of additional doses of cidofovir	Treatment evaluation	Toxicity observed after day 15	Patient status at day 60
Adenovirus					
1	Blood	6	Failure; some response after 2nd dose, but viral load then rapidly increased; +AdV from CSF	None	Deceased secondary to AdV, aGVHD, PRES
3	Blood	0	Failure; rapidly progressive multiorgan failure and death within 10 days of study entry	NA	Deceased secondary to AdV
7	Blood	4	Success; rapid clinical improvement and decrease in viral load; infection was not completely cleared until >100 days posttransplantation	None	Living
8	Blood	1	Success; some improvement after 2nd dose, and infection was eventually cleared by day 60	CKD, stage 5	Living; awaiting renal transplant
9	Blood	1	Failure; disseminated disease with multiorgan failure; no virological response	AKI, failure	Deceased secondary to AdV
10	Blood	6	Success; viral load gradually increased during 1st 4 doses but then improved, and virus was eventually cleared	None	Deceased at 18 mo secondary to relapsed ALL
11	Blood	6	Success; gradual complete clearing of infection in <60 days	None	Living
BK virus					
2	Urine	7	Failure; developed +BK virus from blood and +AdV from stool while on therapy, +AdV from blood shortly after discontinuation of therapy for nephrotoxicity	CKD, stage 3	Deceased at day 90 secondary to multiple viral infections, aGVHD
4	Urine	0	Failure; no response; continued to have persistent BK virus in urine for 2 yr poststudy; +AdV in blood 16 days after cidofovir; infection cleared spontaneously	None	Living
5	Urine	4	Failure; no response in urine, +BK virus in blood while on therapy; CMV load briefly increased and then improved during therapy	None	Living
6	Urine	1	Failure; initially decreased viral load in urine but new +BK virus in blood; CMV load also increased; infection was eventually cleared with foscarnet, ganciclovir, and immune reconstitution	None	Living
CMV					
12	Blood	1	Failure; restarted on CMV IgG (CytoGam) and ganciclovir after 2nd dose of cidofovir and subsequently cleared infection	None	Living

[a] CSF, cerebrospinal fluid; NA, not applicable; CKD, chronic kidney disease; aGVHD, acute graft-versus-host disease; PRES, posterior reversible encephalopathy syndrome; +AdV, positive adenovirus; +BK, positive BK virus.

Virological responses to the study dose of cidofovir are shown in Table 3. Two of the seven patients with adenovirus infection had a significant decrease in viral copy number within 7 days after the first dose of cidofovir; all others had stable or increased levels of viral DNA in blood.

Two of the 12 patients had evidence of acute kidney injury after the first dose, as graded by pediatric-modified RIFLE criteria (27). No additional early adverse events were noted. No subject had a hypersensitivity reaction following cidofovir injection or decreased intraocular pressure at day 6. Ten patients had multiple viral infections diagnosed at study entry or later during the study period, and 3 of the 10 had documented fungal and bacterial coinfections.

Ten patients received additional weekly doses of cidofovir (1 to 7 doses) after receiving the study dose. Response to therapy, later toxicities, and status at the end of the study are presented in Table 4. Four of the seven patients with adenovirus infection were successfully treated and eventually cleared their infections completely. Three patients died of disseminated adenovirus infection and multiorgan failure, including a neuroblastoma patient (patient 3) after autologous HSCT whose adenovirus infection progressed very rapidly and who died of hepatic failure prior to receiving a second dose of cidofovir. One patient (patient 9) developed acute kidney failure prior to death. He had BK virus viruria and viremia and HHV-6 viremia in addition to adenovirus infection. His kidney failure was presumed to be multifactorial and not due exclusively to the two doses of cidofovir that he received.

None of the patients with BK virus or CMV infection successfully cleared their virus on treatment. Three of the four patients with BK virus viruria developed BK virus viremia while receiving additional doses of cidofovir, including one patient (patient 6) whose viruria initially responded. Patient 2 died 90 days after study entry; he was enrolled for BK virus viruria but developed adenovirus infection during the study. He received a total of seven doses of cidofovir before it was discontinued for nephrotoxicity. He had grade 3 chronic kidney disease at the time of his death from disseminated viral infection and multiorgan failure.

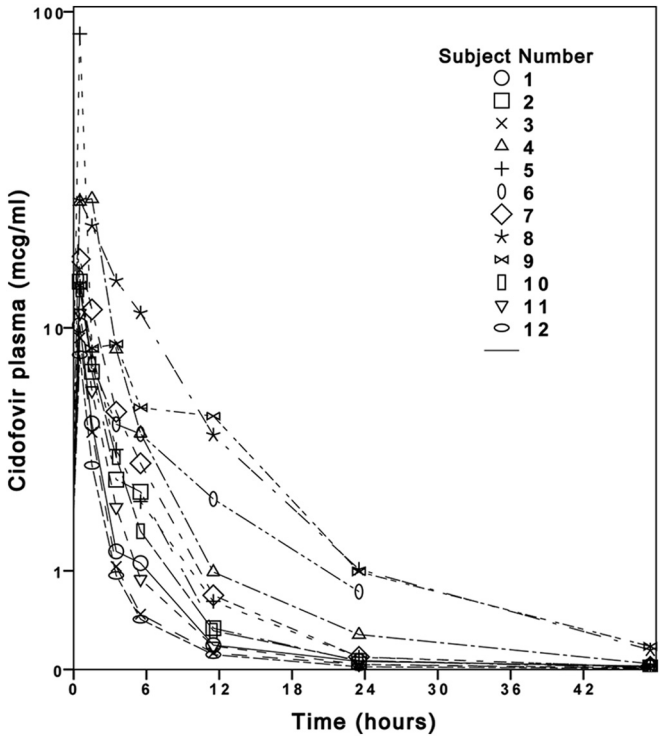

FIG 1 Semilogarithmic plot of plasma cidofovir concentrations versus time for all subjects.

Of the eight patients who were long-term survivors, one patient developed chronic kidney disease, and no other late toxicities were observed. Patient 8 was 111 days posttransplantation at study entry, the latest of any patient, and had been treated with multiple other nephrotoxic medications for chronic GVHD and comorbid bacterial, fungal, BK virus, and CMV infections, although he received only two doses of cidofovir for adenovirus.

Pharmacokinetics of cidofovir. Plasma cidofovir PK data were analyzed for all 12 patients. The plasma concentration-versus-time semilogarithmic plot for all subjects is displayed in Fig. 1. Predicted concentrations from the individual 2-compartment models along with measured data points are shown in Fig. 2. Urine cidofovir data were also collected for seven patients. Figure 3 shows a semilogarithmic plot of the urine concentration versus time. Calculated PK parameters for individual patients, including calculated renal clearance of cidofovir during collection from 720 to 1,440 min, are presented in Table 5. There was no correlation between nephrotoxicity and the maximum concentration of drug in plasma (C_{max}), area under the plasma concentration-time curve from 0 to 2,880 min ($AUC_{0\text{-}2,880}$), plasma or renal clearance, or $t_{1/2}$. The mean half-life was 9.5 h. An additional half-life calculation was done by using data obtained between the 8- and 10-h time points, in order to compare data more directly with data from previously reported PK studies in adults; this gave a mean half-life of 5.8 h (9).

Most pharmacokinetic parameters in our pediatric population were similar those in adults in previously reported studies (9). Cundy and colleagues reported that nonlinear noncompartmental curve fitting produced pharmacokinetic parameters similar to those from a two-compartmental analysis of samples from their first study. This suggests that comparison of our parameters, calculated from two-compartment analysis, to those from previous reports is acceptable. As in adults, we confirmed that cidofovir is cleared primarily via the kidneys. Renal clearance calculated from urine data correlated closely with plasma clearance in each subject. The steady-state volumes of distribution in the present study and in adults were similar, at 591 and 490 ml/kg, respectively. The elimination phase clearance rates in the present study and in adults were also similar, at 2.2 and 2.5 ml/kg/min, respectively. However, there was a marked difference in the terminal elimination half-life. Cundy and colleagues previously reported a half-life of 2.6 h, while the present study found a half-life of 9.5 h (9).

DISCUSSION

While cidofovir may, in fact, have a longer half-life in children, it is important to consider differences in study design that may also be contributory. Half-life can appear falsely short if samples are not collected after the distribution phase is complete. In our study, samples were collected through 48 h, while the adult study, sample collection was stopped after 12 h; when we analyzed data prior to the 12-h time point, we obtained a half-life of 5.9 h, still longer than that reported for adults. Additionally, as the sensitivity of the plasma assay for cidofovir increases, the half-life calculations can also give higher values. The lower limit of quantification for this assay was nearly 3 orders of magnitude lower than that in the previously reported study: 0.5 ng/ml compared to 220 ng/ml. Neither of these differences, however, completely explains the large difference seen, and so we conclude that pediatric subjects likely have longer half-lives than do adults. Further studies should include multiple-dosing PK analysis, as well as comparison of pediatric with adult subjects using the same protocol design and analysis, in order to better define the magnitude of the difference.

Safety. A single dose of cidofovir was well tolerated in a majority of pediatric HSCT recipients. We noted few adverse cidofovir-related events, despite the fact that this patient population is predisposed to nephrotoxicity from prior chemotherapy and concomitant medications and infections. The longer half-life also did not appear to contribute to increased nephrotoxicity.

Only two patients (patients 4 and 8) developed acute kidney injury after a single dose of cidofovir. One patient (patient 4) spontaneously recovered full renal function, while the other (patient 8) went on to develop stage 5 chronic kidney disease and is now awaiting a renal transplant; however, as noted above, he had a course that was complicated by multiple severe infections and chronic GVHD and received only two doses of cidofovir in total. In fact, there was no correlation between the number of doses of cidofovir and the risk of nephrotoxicity. Of two additional patients who developed late nephrotoxicity, only one (patient 2) had treatment limited due to nephrotoxicity (after 7 doses). The other patient (patient 9) developed acute kidney failure immediately prior to death from disseminated adenovirus infection; cidofovir therefore appeared not to be a major contributor to his nephrotoxicity.

Limitations. This study was not designed to establish the efficacy of cidofovir in a small, heterogeneous population of pediatric HSCT recipients. Previously reported studies in this area have consisted of case series and small retrospective observational studies. However, our observations were consistent with data from previous reports of viral infections in the post-HSCT period (13, 18). Most patients in our series had received allogeneic HSCT and

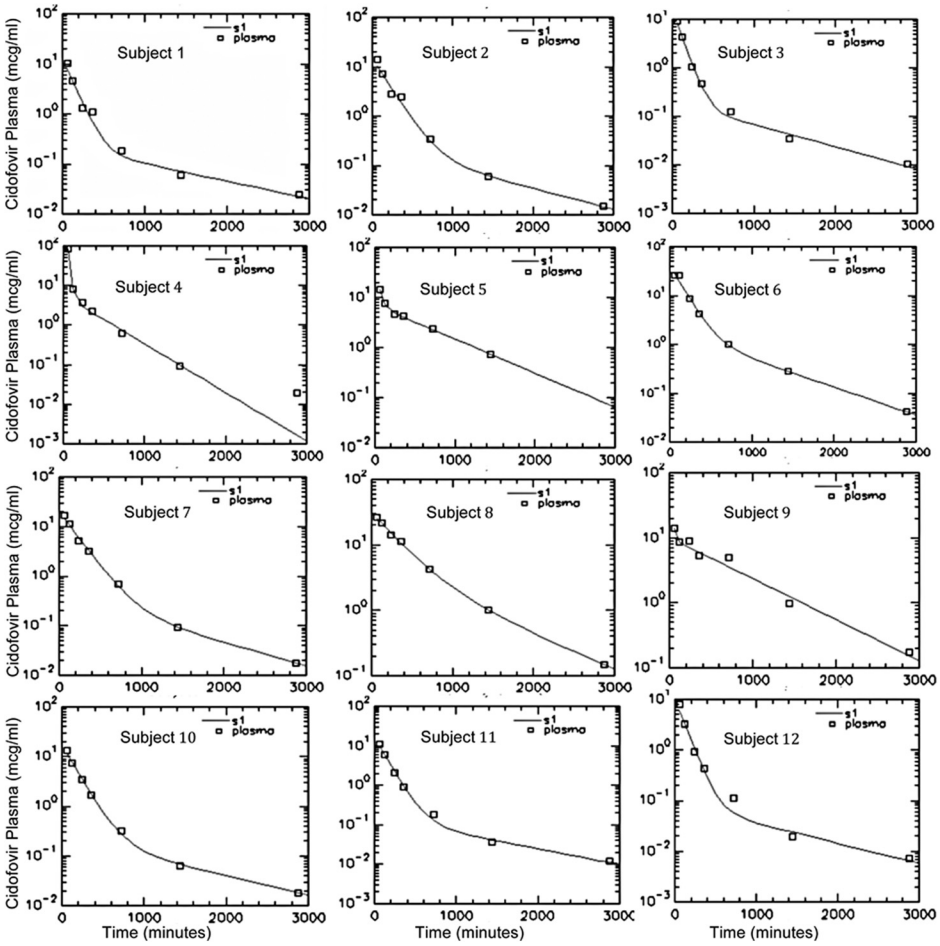

FIG 2 Predicted and measured concentrations determined by 2-compartment models for individual patients.

were presumably more immunosuppressed than recipients of autologous stem cells. In addition, 10 of the 11 allogeneic HSCT patients had also received cord blood, which results in delayed immune recovery and an increased risk for severe posttransplant viral infection compared to recipients of adult stem cell products.

For some patients, it appeared that cidofovir was able to provide temporary control of infection; with time, we presume that these patients were able to reconstitute their immune systems and eventually cleared the virus. However, four patients died of disseminated viral disease despite treatment, a rate higher than those reported in some case series (13). The clinical courses for these patients were heterogenous. One patient (patient 3) had such rapidly progressive adenoviral infection that he died prior to receiving a second dose of cidofovir, despite being an autologous HSCT recipient who was not receiving immunosuppressive medications. Another patient (patient 2) acquired adenovirus while on cidofovir for an initial presentation of BK virus hemorrhagic cystitis; although his continued therapy was limited by nephrotoxicity, he showed no evidence of virologic response after seven doses. Testing to identify mutations conferring drug resistance was not performed in patients whose virologic loads were unresponsive.

These observations strongly support the need for more effective therapeutic options. Although alternative agents and strategies, including brincidofovir (an orally bioavailable lipid conju-

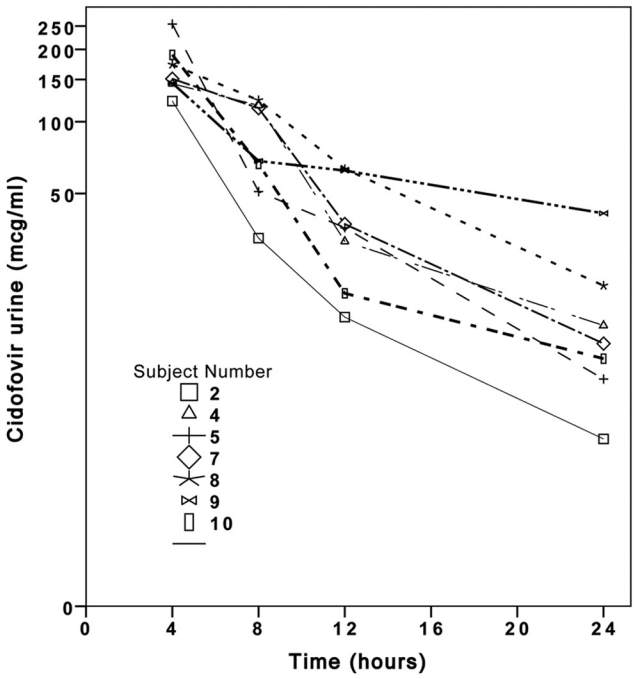

FIG 3 Semilogarithmic plot of urine cidofovir concentrations versus time for all subjects.

TABLE 5 Plasma cidofovir pharmacokinetic parameters and estimated renal clearance rates[a]

Patient	C_{max} (μg/ml)	V_{ss} (ml/kg)	V_1 (ml/kg)	V_2 (ml/kg)	CL_e (ml/kg/min)	CL_I (ml/kg/min)	CL_r (ml/kg/min)	$t_{1/2}$ (h)
1	10.2	1,244	504	740	3.7	0.73		14.1
2	14.2	580	413	167	2.2	0.18	1.1	9.7
3	9.3	930	437	493	4.2	0.60		11.0
4	25.7	232	143	89	0.8	0.14	0.8	8.5
5	85.5	78	20	58	0.7	0.22	1.4	4.1
6	14.6	576	214	362	1.0	3.19		7.4
7	16.8	367	287	80	1.4	0.09	2.0	8.0
8	25.9	226	178	48	0.5	0.07	0.3	7.7
9	13.8	477	170	307	0.7	7.5	0.7	7.9
10	13.4	555	362	193	2.1	0.19	2.5	11.1
11	11.2	668	413	255	3.0	0.28		12.0
12	8.1	1,164	644	520	5.6	0.52		12.6
Mean (SD)	20.7 (20.3)	591 (365)	315 (178)	276 (218)	2.2 (1.6)	0.56 (0.90)	1.3 (0.8)	9.5 (2.8)

[a] C_{max}, maximum concentration; CL_r, calculated renal clearance.

gate of cidofovir) and adoptive transfer of adenovirus-specific donor T lymphocytes, have shown some efficacy, studies have continued to report high mortality rates from adenoviral disease (11, 19–23).

Alternatively, earlier intervention may provide an approach for improving outcomes using existing therapies. Most patients in this study presented with adenoviral enteritis or BK virus hemorrhagic cystitis prior to detection of virus and treatment with cidofovir. Two patients presented with fever and concurrent adenovirus infection detected upon routine weekly PCR screening; both patients fully recovered. While none of the BK virus-infected patients in our study responded to cidofovir therapy, all had severe symptoms and viral loads above the upper detectable limit at study entry. A case series from Finland reported responses in four of five pediatric patients receiving intravenous cidofovir: all patients were identified via surveillance rather than symptoms, suggesting that they were treated early in the disease course, and received both intravesicular and intravenous cidofovir (24). Other studies of adenovirus infection have similarly suggested that cidofovir is most effective when started early (18, 21, 25). Current European guidelines (2011) recommend weekly adenovirus surveillance for all pediatric HSCT recipients with at least one of the following risk factors: T-cell depletion of the graft, unrelated adult donor or cord blood graft, grade III or IV GVHD, and severe lymphopenia (18).

Conclusions. Pharmacokinetic parameters of cidofovir in pediatric patients were similar to those reported for adults, with the exception of half-life, which was significantly longer. Despite the longer half-life, cidofovir appears to be safe in a single dose for pediatric HSCT recipients with life-threatening viral infections, despite heavy pretreatment with nephrotoxic agents, including chemotherapy and other antimicrobial therapy. However, efficacy was limited, and 4 of 12 patients died of disseminated viral infection. Effective therapeutic strategies are urgently needed to support patients until immune reconstitution is achieved.

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